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Altered intraoperative cerebrovascular reactivity in brain areas of high-grade glioma recurrence

Fierstra, Jorn ; van Niftrik, Bas ; Piccirelli, Marco ; Burkhardt, Jan-Karl ; Pangalu, Athina ; Kocian, Roman ; Valavanis, Antonios ; Weller, Michael ; Regli, Luca ; Bozinov, Oliver

Abstract: **INTRODUCTION:** Current MRI sequences are limited in identifying brain areas at risk for high grade glioma recurrence. We employed intraoperative 3-Tesla functional MRI to assess cerebrovascular reactivity (CVR) after high-grade glioma resection and analyzed regional CVR responses in areas of tumor recurrence on clinical follow-up imaging. **METHODS:** Five subjects with high-grade glioma that underwent an intraoperative Blood Oxygen-Level Dependent (BOLD) MRI CVR examination and had a clinical follow-up of at least 18 months were selected from a prospective database. For this study, location of tumor recurrence was spatially matched to the intraoperative imaging to assess CVR response in that particular area. CVR is defined as the percent BOLD signal change during repeated cycles of apnea. **RESULTS:** Of the 5 subjects (mean age 44, 2 females), 4 were diagnosed with a WHO grade III and 1 subject with a WHO grade IV glioma. Three subjects exhibited a tumor recurrence on clinical follow-up MRI (mean: 15 months). BOLD CVR measured in the spatially matched area of tumor recurrence was on average 94% increased (range -32% to 183%) as compared to contralateral hemisphere CVR response, 1.50 ± 0.81 versus 1.03 ± 0.46 respectively ($p=0.31$). **CONCLUSION:** For this first analysis in a small cohort, we found altered intraoperative CVR in brain areas exhibiting high grade glioma recurrence on clinical follow-up imaging.

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Title: Altered intraoperative cerebrovascular reactivity in brain areas of high-grade glioma recurrence

Running title: Altered intraoperative CVR in brain areas of tumor recurrence

List of authors: Jorn Fierstra, MD PhD¹; Bas van Niftrik, MD¹; Marco Piccirelli, PhD²; Jan Karl Burkhardt, MD¹; Athina Pangalu, MD²; Roman Kocian, MD³; Antonios Valavanis, MD²; Michael Weller, MD⁴; Luca Regli, MD¹; Oliver Bozinov, MD¹

Affiliations: Departments of Neurosurgery¹, Neuroradiology², Neuro-anesthesia³, and Neurology⁴, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Switzerland.

Corresponding author:

Jorn Fierstra, MD PhD

Department of Neurosurgery, University Hospital Zurich, University of Zurich,

Frauenklinikstrasse 10

8091 Zurich, Switzerland

Phone: +41-44-2551111

Fax: +41-44-2554505

E-mail: jorn.fierstra@usz.ch

Keywords: functional MRI, Blood Oxygen-Level Dependent, intraoperative, high-grade cerebral glioma, cerebrovascular reactivity.

Abstract

Introduction: Current MRI sequences are limited in identifying brain areas at risk for high grade glioma recurrence. We employed intraoperative 3-Tesla functional MRI to assess cerebrovascular reactivity (CVR) after high-grade glioma resection and analyzed regional CVR responses in areas of tumor recurrence on clinical follow-up imaging.

Methods: Five subjects with high-grade glioma that underwent an intraoperative Blood Oxygen-Level Dependent (BOLD) MRI CVR examination and had a clinical follow-up of at least 18 months were selected from a prospective database. For this study, location of tumor recurrence was spatially matched to the intraoperative imaging to assess CVR response in that particular area. CVR is defined as the percent BOLD signal change during repeated cycles of apnea.

Results: Of the 5 subjects (mean age 44, 2 females), 4 were diagnosed with a WHO grade III and 1 subject with a WHO grade IV glioma. Three subjects exhibited a tumor recurrence on clinical follow-up MRI (mean: 15 months). BOLD CVR measured in the spatially matched area of tumor recurrence was on average 64% increased (range -29% to 123%) as compared to whole brain CVR response, 1.50 ± 0.81 versus 1.09 ± 0.37 respectively.

Conclusion: For this first analysis in a small cohort, we found altered intraoperative CVR in brain areas exhibiting high grade glioma recurrence on clinical follow-up imaging.

1. Introduction

Currently, the best available neuroimaging biomarker for identifying high grade gliomas is conventional contrast-enhanced magnetic resonance imaging (CE-MRI).[1] The ability of obtaining this sequence with intraoperative MRI further enhances resection control by providing a timely evaluation of tumor residual that can be removed additionally. [2-4] CE-MRI sequences, however, are inherently limited to exactly identify tumor borders due to heterogeneous tumor enhancement and cannot assess functional parameters such as tumor molecular biology. Therefore, O-(2-[18F]fluoroethyl)-L tyrosine Positron Emission Tomography, (FET-PET) may potentially better depict high grade glioma tissue, but lower spatial resolution and limited clinical availability are remaining challenges.[5]

Cerebrovascular reactivity (CVR) is a functional parameter that can be assessed with MRI by obtaining Blood Oxygen-Level Dependent (BOLD) volumes. CVR is determined as the BOLD signal response due to deoxyhemoglobin washout related to carbon dioxide (CO₂) changes as the vasoactive stimulus,[6]and can be measured on high spatial resolution covering the entire brain. Using this concept, Hsu et al. [7] have demonstrated that BOLD MRI generates CVR patterns to better distinguish normal brain tissue from glioma tissue. Bashat et al.[8]used BOLD CVR to assess the effect of anti-angiogenesis tumor therapies in subjects with intracranial high-grade gliomas, and found that such an assessment can complement existing MR techniques for better detection and follow-up of angiogenic changes.

The use of intraoperative BOLD CVR for intracranial tumors has not been reported thus far. We hypothesized that intraoperative BOLD CVR is altered in perifocal non-contrast enhancing tissue prone to future tumor recurrence. For this initial study we analyzed five consecutive subjects from an ongoing prospective intraoperative BOLD CVR study that underwent high-grade glioma resection. All subjects were postoperatively followed with

clinical CE-MRI imaging. Three subjects exhibited a tumor recurrence within 2 years of follow-up. The area of tumor recurrence on follow-up CE-MRI was spatially matched with the intraoperative BOLD CVR data to assess CVR response in that particular area.

2. Materials & Methods

2.1 Subject selection

This study was approved by the cantonal ethics board of the Canton of Zurich, Switzerland (KEK-ZH-Nr. 2012-0427). In October 2013 we have started an ongoing prospective study of intraoperative BOLD MRI CVR in subjects undergoing a cerebral glioma resection to assess regional CVR patterns. For this analysis, we selected subjects from this prospective database with high-grade glioma, defined as histopathological type III or IV according to WHO criteria, and a minimum of 18 months follow-up after tumor resection. Five consecutive subjects were found eligible.

The study protocol consisted of an additional BOLD MRI sequence with 3 cycles of apnea (i.e. CO₂ changes) during a scheduled intraoperative MRI examination following tumor resection. All subjects gave signed consent for study participation preoperatively. Subjects that were not able to sign consent were excluded as well as subjects with any predisposing cardio-pulmonary condition requiring special anesthetic care during surgery.

2.2 Intraoperative BOLD MRI imaging protocol

Mechanically ventilated subjects were scanned on a 3-Tesla Siemens Skyra VD13 (Siemens, Erlangen, Germany). Images were obtained using a customized intraoperative 8 channels head coil (NORAS MRI products, Hochberg, Germany), incorporated with a MRI compatible surgical four-point head-fixation system in which the subjects' head was placed at surgery. Whole brain BOLD volumes were collected with an axial 7.20 minute 2D echo planar

imaging (EPI) BOLD sequence with voxel size: $3 \times 3 \times 3$ mm³, acquisition of matrix 64×64 , 35 slices with ascending interleaved acquisition, slice gap 0.3 mm, GRAPPA factor 2 with 32 ref. lines, adaptive Coil Combination, Auto Coil Selection, TR/TE 2000/30 ms, flip angle 85° , bandwidth 2368 Hz/Px, 220 volumes, field of view 192mm x 192mm. For co-registration of the functional sequence, skull stripping and overlay purposes, the anatomical T1-weighted-MPRAGE sequence (Voxel size: $0.5 \times 0.5 \times 0.9$ mm, Field of View read 240 mm, Slice thickness 0.90 mm, TR 1900.0 ms, TE 2.60 ms, Flip angle 9 deg, Base resolution 256, Phase resolution 100 %, Interpolation to 512×512) from the clinical protocol was used. The field of view from the BOLD image acquisition was copied to the T1-weighted image for better early realignment of both images.

2.3 CO₂ stimulus during BOLD acquisitions

BOLD signal changes were made by three cycles of apnea to induce hypercapnia (ie. higher CO₂ levels) under direct neuro-anesthetic monitoring. During the first 88 second, regular mechanically ventilated breathing was continued to provide a baseline, after which a 44 second apnea - breath hold - period was initiated by halting the ventilator. After apnea the subject was manually hyperventilated to swiftly return to baseline CO₂ value. In total, 3 identical series of 44 seconds apnea were done during the BOLD sequence with an interval baseline period of 88 seconds. A 44 second apnea paradigm is expected to provide a robust CO₂ change within physiological range. [9] Furthermore, following standard clinical management during intraoperative MRI examinations at our institution, subjects were continuously monitored by our neuro-anesthetic team.

2.4 Data analysis

The images were preprocessed using Statistical Parameter Mapping software (SPM 12, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College

London; <http://www.fil.ion.ucl.ac.uk/spm/>). A mean BOLD volume was calculated and the T1-weighted image was linearly registered to this volume. Automated segmentation of the T1-weighted image generated grey and white matter, cerebrospinal fluid, skull and skin probability maps. The BOLD images were smoothed with an 8x8x8-mm full width half maximum Gaussian kernel. Due to the four point head fixation, we assumed minimal head motion could occur during the MRI acquisition. Therefore, correcting for head-motion in realignment was not considered necessary. Temporal smoothing included a low pass filter of 0.125Hz and robust Loess smoothing (dynamic local regression of 6%).

2.5 Cerebrovascular reactivity maps

MRI volumes were analyzed using in-house scripts written in MATLAB2013 (The MathWorks, Inc, Natick, United States; <http://www.mathworks.com/>). MR time-courses were detrended by fitting a linear series to the data. A Sine wave was created with a separate frequency for the apnea period and ventilation period. To increase Coherence, we calculated the maximum Pearson product-moment correlation and shifted the Sine wave to its best fit with the BOLD data on a voxel-wise base. After applying a combined grey and white matter mask with a threshold of 0.9, CVR, defined as the percent BOLD change, was then calculated using a voxel-wise linear regression of BOLD time series versus the Sine wave with least square fitting.

The resected tumor area matched the signal intensity of CSF and was automatically not included in the calculations. Hemispheres were manually segmented in left and right hemisphere and CVR was calculated separately for both. CVR maps were color-coded and overlaid on the T1-weighted image (Figure 1).

2.6 Extended analysis

2.6.1 Intraoperative residual tumor

An experienced staff neuroradiologist (A.P.) determined the presence of residual tumor on intraoperative clinical MRI. When present, we extracted the T1-CE and T2 fluid-inversion attenuated recovery (FLAIR) images to perform an automated delineation analysis. In summary, first, to align the images a linear registration was done using the T1-weighted image as the reference. Both T1-weighted images were normalized to their mean and standard deviation on a voxel-wise base which has been shown to improve contrast to noise in the images. [10] Thereafter, the normalized T1-CE was subtracted from the normalized T1-weighted to create the subtraction map (Figure 2).

To determine pathological voxels, the FLAIR image was aligned with the subtraction image and normalized in a similar manner as both the T1-weighted images. After evaluation of these normalized maps, it was decided to threshold the FLAIR image at a fixed value of 5 to generate a binary mask only including voxels with FLAIR signal hyperintensities. To finally delineate the residual tumor, the binary FLAIR mask and a combined grey and white matter mask (Threshold 0.9) were placed over the normalized subtraction map (Figure 1C). This allowed for exclusion of physiological contrast-enhanced regions (large arteries, meninges) as well as exclusion of voxels outside of the brain. Voxels within the delineated tumor map with a positive Δ signal increase (voxels increasing in intensity after administration of contrast) were included for further evaluation.

2.6.2 Tumor recurrence

Based on standard clinical CE-MR imaging during follow-up, the presence of tumor recurrence was evaluated by an experienced staff neuroradiologist. In two subjects, an additional histopathological analysis of tumor recurrence was possible due to second surgical tumor resection. Similar to the tumor residual, a tumor mask of the tumor recurrence was created by automated delineation analysis.

With the use of the T1-weighted volume, the tumor mask was coregistered to the intraoperative volume (Figure 1C). Thereafter, the tumor mask was placed over the CVR map to locate regions of recurrence on the intraoperative CVR map. Subsequently CVR in those regions was calculated.

3. Results

3.1 Subjects

Of the five eligible subjects (mean age 44, range 38-51, 2 females), 1 subject had a WHO grade IV and 4 a WHO grade III cerebral glioma (Table 1). All gliomas were located in the left frontal region. The mean postoperative follow-up was 24 months \pm 2.0. Three subjects exhibited a tumor recurrence on follow-up CE-MRI imaging at an average of 15 months (range 11-18).

3.2 Cerebrovascular reactivity findings

Whole brain CVR, and CVR for both hemispheres separately are presented in Table 2. Mean CVR in the ipsilateral hemisphere vs. the contralateral hemisphere did not differ significantly ($p=0.4$).

3.2.1 Residual tumor on intraoperative CE-MRI

Three subjects had a residual tumor on intraoperative CE-MRI which was subsequently further resected during the same surgery. CVR in the area of residual tumor was 1.87 ± 0.53 on average as compared to whole brain CVR 1.09 ± 0.37 , a 122% mean CVR increase (Table 2).

3.2.2 Tumor recurrence on follow-up clinical CE-MRI

Tumor recurrence was found in three subjects on CE-MRI. The area of tumor recurrence was spatially matched to the intraoperatively acquired BOLD CVR data. CVR in the area of tumor

recurrence was 1.50 ± 0.81 . This was considerably different from whole brain CVR, 1.09 ± 0.37 , an overall 64% CVR increase (Table 2).

The tumor recurrence in subject 1 (Table 2) was decided not to be resected surgically but treated with a second round of chemotherapy in combination with Bevacizumab. The area of tumor recurrence, which was spatially matched to the intraoperative BOLD-CVR map (Figure 1), exhibited a 29 % CVR decrease as compared to whole brain CVR, 0.90 vs 0.64 respectively. The other two subjects underwent a second surgical tumor resection with histopathological analysis showing a recurrence of an anaplastic astrocytoma WHO grade III and glioblastoma WHO grade IV (subject 3 & 4 respectively; Table 2). For subject 3, no contrast enhancement was seen on T1, but diagnosis of recurrence was made based on FLAIR T2 imaging. Interestingly for this subject, after subtraction of the non-contrast enhanced T1-weighted from the CE-T1-weighted images (see methods), a contrast enhanced tumor area was found matching the FLAIR enhancement (Figure 2). The area of tumor recurrence for this subject was 123% increased as compared to whole brain CVR (1.01 vs. 2.26). CVR values for subject 4 were 0.85 vs. 1.60; a 99% CVR increase (whole brain vs. recurrence).

4. Discussion

Our preliminary findings in a small cohort (n= 5) demonstrate that intraoperative BOLD MRI provides feasible CVR measurements in subjects undergoing resection of high-grade cerebral glioma. Of the five subjects included, three developed a tumor recurrence on follow-up imaging (average duration from surgery to recurrence was 15 months). The area of tumor recurrence at follow-up was spatially matched onto the intraoperative BOLD CVR data acquired at the first surgery (see methods section). In this area of tumor recurrence, CVR was 1.50 ± 0.81 vs. 1.09 ± 0.37 for whole brain, corresponding to a mean CVR increase of 64%. No significant CVR differences were found between the ipsi- and contralateral hemispheres, indicating a marked regional CVR change in the area of tumor recurrence.

4.1 Significance of CVR in high-grade glioma

MR-based imaging modalities assessing cerebrovascular autoregulation and CVR have not been explored widely for high-grade cerebral glioma. This may be related to heterogeneity of the disease, posing methodological challenges on acquiring useful functional imaging information. Preliminary studies on human subjects suggest that BOLD CVR may be a potential tool to distinguish between normal brain tissue and cerebral glioma. This may hold great promise since one of the largest remaining challenges of current conventional MRI techniques is better depiction of tumor margins. Moreover, a BOLD-CVR examination may even differentiate between low-grade versus high-grade gliomas. For instance, in a small series reported by Hsu et al.[7] steal phenomenon was found in high-grade gliomas, an observation not made in low-grade gliomas. The authors hypothesized that under hypercapnic stress, blood from a region of the tumor in which the vessels do not dilate due to abnormal angiogenesis is redistributed to a responsive tumor region and surrounding normal tissue, causing a focal steal phenomenon with decrease of tumor perfusion. The steal phenomenon is expected to be exaggerated in a tumor region where cellularity is high (greater oxygen demand) and neovascularization is marked (absent CO₂-induced vasodilatation), resulting in reduced BOLD signal. Bashat et al.[8] used BOLD CVR to assess the effect of anti-angiogenesis tumor therapies in patients with cerebral high-grade glioma. Termed hemodynamic response imaging, the authors conclude that such an assessment can complement existing MR techniques for better detection and follow-up of angiogenic activity.

Animal studies have elaborated on the same findings. For instance Laufer et al.[11] assessed the hemodynamic response in a rat model with glioblastoma to verify its use in gauging effect of anti-angiogenesis therapy. Jerome et al.[12] utilized the 9L rat glioma model mimicking an aggressive intracranial high-grade glioma, to determine that BOLD CVR measures can

differentiate between core and rim zone tumor tissue. This may have potential use for differentiating the heterogeneous nature of high-grade gliomas on imaging.

Another potential future application is the combined assessment of BOLD CVR in relation to visual, speech or sensorimotor task-based fMRI in brain eloquent areas. Currently, pre-surgical task-based fMRI assists the neurosurgeon in identifying proximity of brain eloquent areas in patients with brain gliomas. A significant limitation of task-based fMRI, however, is false negative activation, termed neurovascular uncoupling.[13, 14] Here, the neurons are indeed signaling (ie. the subject performs a task, such as fingertapping), resulting in a BOLD signal change. When impaired CVR is present in these areas (something that cannot be assessed with conventional task-based BOLD fMRI) the BOLD signal change does not follow the expected signal increase, and may even be paradoxically decreased. Standard thresholding applied to task-based fMRI may therefore exclude such viable brain tissue, i.e. false negative activation, which may result in undesirable surgical resection and therefore irreversible neurological deficits. For such patients a supplementary BOLD-CVR examination may differentiate whether impaired CVR is present in brain eloquent areas, where neuronal viability can then be verified with for instance intraoperative direct electro-cortical stimulation mapping.

We have developed a practical intraoperative BOLD-MRI + CO₂ protocol that generates feasible regional and whole brain CVR measurements. The resulting BOLD CVR map was used as a functional overlay on the automatically segmented tumor recurrence masks as described in the methods section. Our CVR findings were quite heterogeneous, which may be indicative of heterogeneity of disease. The intraoperative tumor residual showed a trend towards increased CVR (mean CVR increase of 122%). Overall the intraoperative regional CVR in the areas of tumor recurrence was 64% higher as compared to whole brain CVR.

However there was heterogeneity in the results. One subject exhibited a CVR decrease of -29%. This CVR decrease could represent underlying steal phenomenon in occult tumor tissue. This may be the result of increased angiogenesis resulting in abnormal vessels with failing autoregulation as has also been hypothesized by Hsu et al.[7] The marked increased CVR found in the other two subjects seems in contradiction with the previous theory of steal phenomenon and mandates a different explanation. Such an increase may be representative of a latent state of controlled hypervascularization due to underlying high metabolic activity, i.e. elevated oxygen demand –and increased cerebral blood flow. Here, we have to assume that tumor cells may be active in this tissue, however, not yet in an uncontrolled manner (i.e. no contrast enhancement and no steal phenomenon). Since there is no contrast enhancement, such a state may mimic a situation similar to a lower grade tumor stage before developing into more malignant. In their paper, Hsu et al.[7] directly hinted to such a possibility by reporting that steal phenomenon was not found in subjects with low grade glioma. Another explanation may be that after tumor resection a state of local hyperreactivity occurs, since the source of high blood flow demand (the tumor mass) has been taken away and the surrounding blood vessels have to adapt to less blood flow demand. Clearly these hypotheses remain purely speculative.

4.2 Limitations & future considerations

These are preliminary findings and have to be interpreted with caution. First of all, our subject sample is small, therefore, limiting interpretation. At best we can report a trend of CVR increase in areas of tumor residual and recurrence. Nevertheless, with improved post-processing analyses and automated determination of tumor area we were able to derive a robust global and regional CVR assessment.

Regarding the subject sample size, these datasets were obtained from an ongoing prospective study of intraoperative BOLD MRI CVR measurements in subjects undergoing an intracranial glioma resection to assess regional CVR patterns. Since we commenced this study in 2013, we only found 5 subjects eligible. Although a small number of subjects, the substantial CVR differences in areas of tumor recurrence provide encouraging results that deserve to be reported as preliminary results. We continue to study BOLD CVR as potential prospective imaging biomarkers for high grade glioma recurrence.

Future considerations are ongoing subject enrollment, longer follow up and further standardization of the BOLD CVR technique to obtain quantitative data.⁶ Improvements of BOLD CVR methodologies have been proposed[13, 15] and may increase sensitivity and quantification of (regional) CVR measurements in subjects with high-grade cerebral glioma. Also, a preoperative BOLD CVR assessment may further our understanding of CVR response in high grade glioma tissue and may allow for a better comparison of regional CVR response in areas of tumor recurrence.

5. Conclusions

For this first analysis, we explored the application of intraoperative BOLD MRI CVR in a small series of subjects undergoing high grade glioma resection. The results demonstrate altered intraoperative CVR in brain areas of future tumor recurrence.

Disclosures

The authors report no conflict of interest related to this work.

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We like to express our gratitude to the neuro-MRI technicians and neurosurgical operating team of the University Hospital Zurich for their help with the data acquisition.

Figure legends

Figure 1: Tumor recurrence, tumor mask & cerebrovascular reactivity map

Caption Figure 1: Images presented in coronal orientation demonstrating the tumor cavity on the left frontal basis (1A, green arrows) with a clear demarcated contrast enhancing tumor recurrence on clinical follow-up imaging (1B, yellow arrow). The area of tumor recurrence was masked using the automated T1 tumor delineation method as described in the methods section, creating a tumor mask (1C, green) for which CVR was measured and compared to whole brain CVR (1D). Here CVR is color-coded, ranging from red (normal CVR)-yellow-green-blue (severely impaired CVR) and projected on the T1-weighted anatomical intraoperative volume as a functional overlay.

Figure 2: Automated T1-weighted tumor subtraction mask

Caption Figure 2: Illustrative example of the automated T1-weighted tumor subtraction mask. Images are presented in coronal orientation. The mask was created by subtracting the CE-T1-weighted image from the noncontrast T1-weighted image (methods). Interestingly, although the tumor (a WHO grade III anaplastic astrocytoma) did not exhibit contrast enhancement on the CE-T1-weighted volume (2A versus 2B, yellow arrows), the T1 subtraction map did clearly demarcate tumor recurrence (2C) spatially matching the area of hyperintensity on T2-FLAIR imaging (2D).

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Table 1: Subject demographics, tumor characteristics & follow-up

Subject	Age	Sex	Histology	WHO	Tumor location	Tumor recurrence	Time after surgery (m)	total follow-up (m)
1	38	M	anaplastic astrocytoma	III	left frontal	(+)	17	25
2	41	F	anaplastic oligoastrocytoma	III	left frontal	(-)		24
3	43	M	anaplastic oligoastrocytoma	III	left frontal	(+)	18	25
4	51	M	glioblastoma recurrence	IV	left frontal	(+)	11	26
5	46	F	Anaplastic astrocytoma	III	left frontal	(-)		21

**Abbreviations: m = months*

Table 2: Cerebrovascular reactivity findings

Subject	Cerebrovascular reactivity (CVR)*						
	Whole brain	Ipsilateral hemisphere	Contralateral hemisphere	Residual tumor	% alteration from whole brain CVR	Future tumor recurrence**	% alteration from whole brain CVR
1	0.90	0.83	0.94			0.64	-29%
2	0.95	1.02	0.89	1.27	33%		
3	1.01	1.24	0.8	2.28	124%	2.26	123%
4	0.85	1.01	0.69	2.06	208%	1.60	99%
5	1.77	1.62	1.83				
Mean (±SD)	1.09 (0.37)	1.14 (0.30)	1.03 (0.46)	1.87 (0.53)	122%	1.5 (0.81)	64%

* CVR is defined as the percentage BOLD signal change

** The area of future tumor recurrence was projected retrograde on the intraoperative volume to determine intraoperative CVR for that area (methods)

Figure legends

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Caption Figure 1: Images presented in coronal orientation demonstrating the tumor cavity on the left frontal basis (1A, green arrows) with a clear demarcated contrast enhancing tumor recurrence on clinical follow-up imaging (1B, yellow arrow). The area of tumor recurrence was masked using the automated T1 tumor delineation method as described in the methods section, creating a tumor mask (1C, green) for which CVR was measured and compared to whole brain CVR (1D). Here CVR is color-coded, ranging from red (normal CVR)-yellow-green-blue (severely impaired CVR) and projected on the T1-weighted anatomical intraoperative volume as a functional overlay.

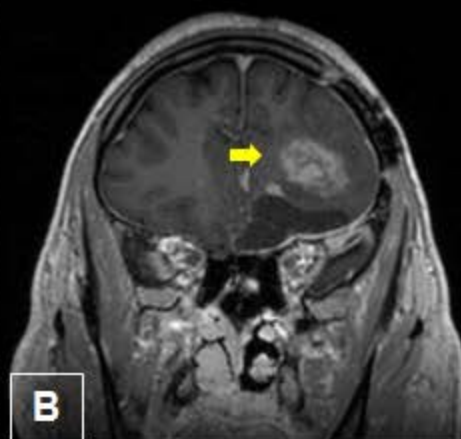
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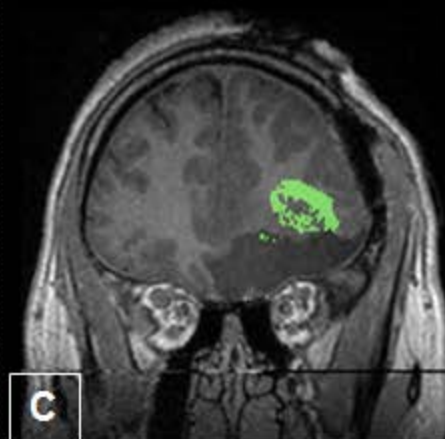
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intraoperative**



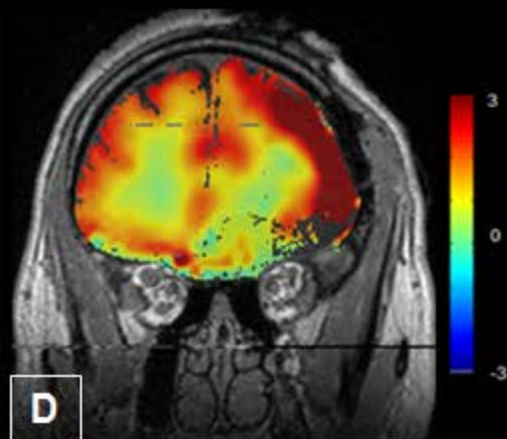
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tumor recurrence**



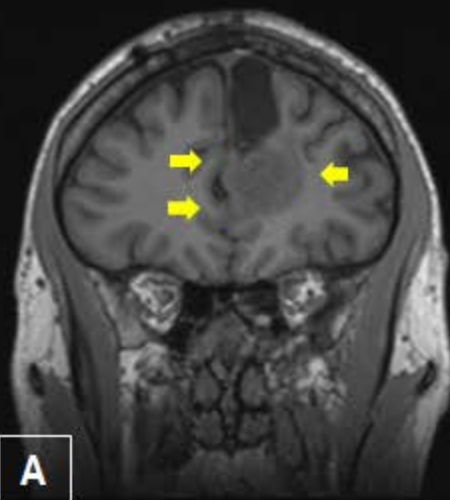
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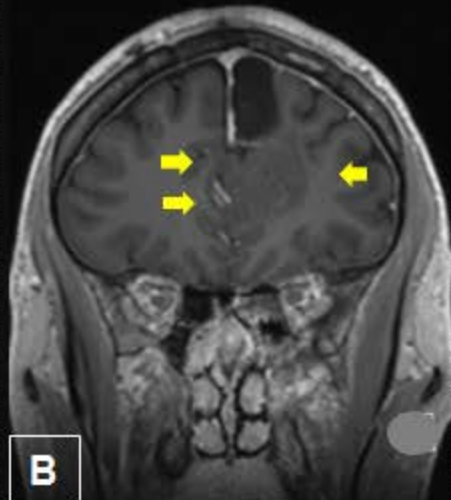
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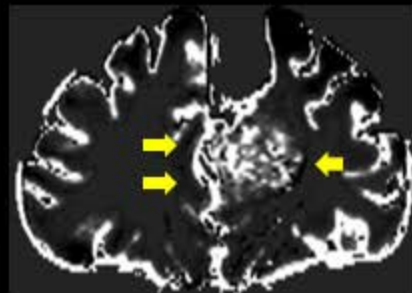
T1 non contrast



T1 contrast



T1 Subtraction



T2 FLAIR

